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Influence of implantation site and track geometry on the extrusion rate and pharmacology of testosterone implants

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Summary

BACKGROUND Implantation of testosterone pellets under the lateral abdominal wall skin is an old but popular and effective form of androgen replacement therapy. Extrusion of one or more pellets remains the most frequent adverse event.

OBJECTIVE To determine whether an alternative implantation site (hip) and/or track geometry (two *vs.* four tracks) would reduce extrusion rates compared with the standard of a four-track abdominal site. Additionally, the study aimed to evaluate the effects of site and track geometry on other adverse effects (bruising, infection) and the pharmacology of testosterone release from the implants.

DESIGN A prospective, parallel-group unmasked study design in a single centre. The primary objective was to evaluate sites, with evaluation of track geometry a subordinate objective made necessary by anatomical differences. Accordingly, androgen deficient men requiring testosterone implantation with the standard dose (four 200 mg pellets) were randomized into one of three groups (ratio 1 : 1 : 2): a four-track abdomen site (standard), a two-track abdomen site or a two-track hip site. The pharmacological substudy was to evaluate the impact of site and track geometry on testosterone implant pharmacology by monthly hormone assays following implantation.

PATIENTS Two hunded and forty-six implantation procedures involving 96 androgen deficient men.

MEASUREMENTS The primary end-point, extrusion rate per procedure, and secondary end-points (bruising or infection post procedure) were evaluated prospectively by self-report from the participants, and verified when they returned next for implantation. The pharmacology substudy involved monthly blood sampling for hormone (total and free testosterone, LH, FSH) measurements.

RESULTS The extrusion rate was significantly higher [odds ratio (OR) = 2·6, 95% confidence interval (CI) 1·1–7·1] for the hip site (15/125, 12%) compared with the abdominal site (6/121, 5%). Track geometry made no significant difference (OR = 1·05, 95% CI 0·2–5·4) to the extrusion rate. No secondary end-points (bruising, infection) were significantly different according to either site or track geometry. One operator who performed the implant procedures had significantly less primary and secondary adverse events than the other operators ($P = 0·006$). Neither implantation site, nor track geometry influenced pharmacokinetics [peak plasma total and free testosterone concentrations and net hormone release (area-under-curve, AUC)] or pharmacodynamics [nadir plasma LH and FSH and net suppression (AUC) in men with hypergonadotrophic hypogonadism].

CONCLUSIONS We conclude that the hip site has a higher extrusion rate than the standard abdominal wall site but that track geometry does not increase the risk of extrusion. Neither implantation site, nor track geometry influenced either other adverse effects or the pharmacokinetics or pharmacodynamics of testosterone pellet implants.

The pharmacological features of testosterone of most salient clinical relevance are its short duration of activity parenterally and negligible oral bioavailability (Handelsman, 2000). Hence, development of effective androgen replacement therapy for convenient, life-long usage required development of practical therapeutic modalities to overcome these limitations. Those developed include orally active synthetic androgens and depot testosterone formulations. Most synthetic oral androgens, however, belong to the class of hepatotoxic 17α-alkylated androgens (Ishak & Zimmerman, 1987) considered unsuitable for long-term androgen replacement therapy in otherwise healthy young men (Conway *et al*. 2000). The most widely used depot testosterone

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formulation consists of one or more testosterone esters injected intramuscularly in 1–2 ml of vegetable oil vehicle at 2–3 week intervals. While this short-term depot delivery system is the most widely used, it is not popular among androgen deficient men who have experienced alternatives due to the frequency of uncomfortable deep intramuscular injections and the large fluctuations in testosterone concentrations causing unpleasant mood swings in some men (Mackey *et al*., 1995). Newer testosterone formulations with longer duration of action in development include testosterone undecanoate (Zhang *et al*., 1998), testosterone buciclate (Behre & Nieschlag, 1992) and biodegradable testosterone microspheres (Bhasin *et al*., 1992). These promise to maintain physiological testosterone concentrations for 30–70 days following intramuscular injection but none are yet available and they feature large injection volumes (4–8 ml) which may detract from their acceptability. Transdermal patches (Place *et al*., 1990; Meikle *et al*., 1992) or gels (Wang *et al*., 1998) require daily administration and their tolerability may be limited by dermal irritation or messiness, respectively, as well as the inconveniently frequent administration for life-long usage. True long-acting depot testosterone formulations are few and, apart from radiation-polymerized testicular prostheses that release testosterone over 48 months (Imai *et al*., 1997), only testosterone pellet implants (Handelsman, 1998) are in regular use.

Testosterone pellet implants maintain physiological blood testosterone concentrations for 4–6 months after a single administration (Handelsman *et al*., 1990, 1998). In regular clinical use, implants are an effective and popular modality for androgen replacement therapy as indicated by high continuation rates (Handelsman *et al*., 1997). Adverse effects from the office implantation procedure, or subsequently, are uncommon consisting mainly of extrusions (8–10% per procedure) with bruising, infection and fibrosis being much less common (Handelsman *et al*., 1997). Extrusions characteristically occur at approximately 2 months postimplantation with a sterile, foreign-body-like reaction leading to expulsion of one or more pellets via the insertion site. Extrusions are inconvenient, uncomfortable, wasteful and could compromise testosterone delivery. We previously showed that a simple washing procedure to remove potentially adherent surface particles failed to influence extrusion rate (Kelleher *et al*., 1999). The present study was prompted by a report that the hip site for implantation produced no extrusions in a small study of adolescents (Zacharin & Warne, 1997). It was therefore our hypothesis that using a hip site for implantation rather than the standard abdominal site would decrease the extrusion rate.

Patients and methods

Design

The study had a prospective, parallel-group unmasked design. Androgen deficient men about to undergo implantation of four 200 mg testosterone pellets were offered randomization into one of three groups. Group 1 was the standard four-track abdominal implantation, group 2 was a two-track abdominal implantation and group 3 was the two-track hip implantation. Randomization was in the ratio of 1 : 1 : 2, reflecting the primary interest in site with the track geometry being a subordinate variable. The study could not have a fully balanced design due to the anatomical limitation that a four-track hip insertion is not anatomically feasible.

The primary outcome variable was extrusion rate per group. The secondary end-points were other adverse effects notably bruising, infection or any other adverse effect during or after implantation. Outcomes were evaluated prospectively by both subject's self-report (they were asked to telephone in the event of any adverse event) and confirmed retrospectively by systematic questioning of all participants when they returned for their next implantation procedure. In the event of an extrusion, participants were asked to record the date and return the extruded remnant.

Men willing also to provide monthly blood samples were also recruited for the pharmacological substudy which aimed to determine whether implantation site or track geometry influenced the pharmacokinetics, or pharmacodynamics, of testosterone release from the pellets.

Power and sample size

The primary end-point was the extrusion rate for which the standard in this centre has been 8·5% (Handelsman *et al*., 1997). Assuming a one-tailed α of 0·05, a study aiming to detect a 50% decrease in extrusion rate (the minumum regarded as practically significant) requires 110 men per group for a power of 80% and 180 per group for a power of 90%. For a reduction to one-third of the usual extrusion rate, a sample size of 50 per group provides a power of 80% and 80 per group a power of 90%.

Subjects

Subjects for the study were men who presented for routine testosterone replacement therapy. They were each provided with a detailed explanation of the study and an information sheet, after which they signed an informed consent if they elected to be randomized. The study was approved by the hospitals Ethics Review Committee.

Procedures

Implantation procedures were performed by experienced operators and scheduled essentially at random with regard to

the patients. Abdominal implantation was performed through an incision in the skin of the lateral abdominal wall lateral to, and at the level of, the umbilicus as described previously (Handelsman, 1998). Hip implantation was performed through a skin incision 3–4 cm below the level of the superior iliac crest on the lateral convexity of the gluteal region so that the insertion site was usually placed below the line of the underwear. All implantations were performed under clean conditions for minor office surgery. The insertion site was routinely swabbed with alcohol with or without povidone–iodine, covered with a fenestrated sterile drape and the line of the intended tracks were infiltrated with 5–10 ml of 1% xylocaine depending on whether two or four tracks were used. A 1–2 cm incision was made in the anaesthetized skin through which the subdermal tracks for implantation were made using a sterilized, stainless steel trochar, cannula and obturator set. Pellets were delivered to lie either individually or end-to-end in pairs at the distal end of the tracks. Following implantation, incision bleeding was stopped by digital pressure and the site was then covered with sterile adhesive strips (for abdominal site) or with a single silk suture (for hip site) followed in all cases by a waterproof outer dressing. The waterproof dressing was removed after 1 week when incision had healed. Those having a suture were instructed how to remove it.

Assays

Hormone assays were performed in a single laboratory as described previously (Handelsman *et al*., 1990, 1995, 1996, 2000). Plasma LH (Axsym, Abbott Laboratories, North Chicago, IL, USA; CV 5·0–7·4%), FSH (Axsym, Abbott Laboratories; CV 3·5–7·4%), total testosterone (DPC, Los Angeles, CA, USA; 7·8–12·7%) were measured by commercial immunoassays. Free testosterone was measured by an in-house centrifugal ultrafiltration assay (CV 9·6–11·7%) using Centrifree columns (Millipore, Milford, MA, USA) and tritiated testosterone to estimate percentage unbound testosterone from which actual free testosterone is calculated using total testosterone concentration.

Statistical analysis

All data was expressed as mean ± SEM and analysed using SPSS version 8·0 (Chicago, IL, USA) with graphs created by Sigmaplot Version 5. Categorical data were analysed by Fisher's exact test and continuous data by *t*-tests or ANOVA as appropriate. Pharmacokinetic data was analysed by standard methods (Gibaldi & Perrier, 1982; Minto *et al*., 1997).

Table 1 Characteristics of study participants

	Abdomen	Hip	*P*
n	121	125	
Age (years)	46·6 ± 2·2	47·4 ± 3·8	0·82
Height (cm)	178·8 ± 5·1	181·4 ± 4·9	0·75
Weight (kg)	80 ± 3·6	80 ± 4·4	0·72
Type of hypogonadism			
Hypergonadotrophic (%)	80 (66%)	74 (59%)	0·54
Baseline hormones			
Testosterone			
Total (nM/l)	9·1 ± 2·1	10·8 ± 0·9	0·64
Free (pM/l)	171 ± 4	190 ± 9	0·65
LH (IU/l)*	15 ± 5·1	13·3 ± 7	0·77
FSH (IU/l)*	22 ± 9·9	20 ± 10·1	0·84

*Includes only men with hypergonadotrophic (primary) hypogonadism.

Results

During the 18 month study period, 96 androgen deficient men about to undergo 246 implantation procedures agreed to participate in the study from 369 consecutive eligible procedures. The overall sample size of 246 therefore has power of approximately 85% to detect a decrease in extrusion rate by at least 50%, which would be regarded as the minimum to change routine practices. The groups were well matched for physical and diagnostic variables (Table 1).

Refusal to be randomized was virtually always due to the desire to choose the implantation site. Consequently, the rate of refusal to be randomized increased during the study as men developed a preference for one particular site. Willingness to be randomized declined from the start of the study [e.g. months 1–3, 42/44 (95%)] to later in the study [months 11–16, 86/146 (59%); OR = 14·65, 95% CI 3·5–128]. Among men refusing to be randomized for having a prior preference for implantation site, twice as many chose the abdominal compared with hip site (80 *vs.* 40, OR = 2·0, 95% CI 1·4–3·0).

Thirty-two men experienced an adverse event in the course of the study, of which three men had an adverse event following two of their implant procedures: one subject had extrusion on two occasions, one had two infections, and the last had an extrusion and a postprocedural bruise. The extrusion rate for the hip site was significantly higher (15/125, 12%) than the abdominal site (6/121, 5%), whereas track geometry made no significant difference to the extrusion rate (Table 2). The rate of extrusion, infection and bruising from both groups remained constant throughout the course of the study (data not shown). The prevalence of the usage of antibiotics in this study was 2·4% overall. None of the secondary endpoints showed any difference according to site or track geometry (Table 2). Furthermore, there was no

Table 2 Events and odds ratios for adverse events

		Abdomen			
	Hip (n =125)	(Two-track) (n =59)	(Four-track) (n =62)	Hip *vs.* abdomen OR (CI)	Two- *vs.* four-track OR (CI)
Extrusion	15	3	3	2·6* (1·2 7·1)	1·05 (0·2–5·4)
Infection	7	4	1	1·4 (0·4–5·7)	0·25 (0·03–2·0)
Antibiotic usage	4	2	0	1·9 (0·3–22)	0·6 (0·1–7·0)
Bruising	1	1	3	1·2 (0·3–6·3)	1·5 (0·4–6·2)

relationship between batch number ($n = 11$) and extrusion (data not shown). There was, however, a difference in extrusion rate between operators. One operator, the most experienced, had significantly fewer extrusions and secondary adverse events than the other operators (Table 3). The excess of hip extrusions was consistent across all operators so that excess extrusions were related to site and not to operator.

There were no significant differences in the baseline levels of total and/or free testosterone across the three groups. Peak concentrations for total and free testosterone occurred at the first month post implantation. The net release (area-under-curve; AUC) of total and free blood testosterone concentrations did not differ significantly between groups (Table 4 and Fig. 1). Figure 1 depicts the mean and SEM values of total and free testosterone over the time course of the study, from baseline to month 6, there are no statistical differences between these groupings. Among men with hypergonadotrophic hypogonadism, there were no differences in baseline or nadir plasma LH or FSH concentrations nor in their net suppression (AUC; Table 4). Nadir gonadotrophin concentrations also occurred uniformly at month 1 for all groups.

Discussion

The ideal form of androgen replacement therapy for young men requiring life-long treatment would be highly effective and safe with a convenient, infrequent and noninvasive manner of administration. Despite the availability of testosterone for over six decades (Hamilton, 1937), no ideal formulation is yet available (Handelsman, 2000). Among the alternatives, where they are available, testosterone pellet implants are a popular and convenient modality of androgen replacement therapy with a particularly long duration of action but with extrusions being an important nuisance adverse event. In a prospective, randomized controlled clinical trial, we previously showed that a topical rinse procedure does not reduce extrusion rate (Kelleher *et al*., 1999).

A retrospective review has shown that physical activity was the only identifiable predisposing factor to extrusion (Handelsman *et al*., 1997). The present study demonstrates that the hip site for the implantation of testosterone pellets has a higher rate of extrusion compared with the standard abdominal site. Among the possible explanations for this are that the hip site is more susceptible to mechanical traction or tension in subdermal tissues associated with hip flexion, leading to irritation which predisposes to extrusion. Anecdotally, participants reported that the hip site was more likely to experience trauma during regular daily activities. An alternative is that our relative inexperience with hip site implantation may have led to a flawed implantation technique. This is unlikely as (i) our hip site technique was established prior to the study to be identical with that described by Zacharin & Warne (1997) by a site visit and (ii) the extrusion rate from the hip site remained consistent throughout the 18 months of the study. Whether the discrepancy from the previous report is due to differences in the ages of the patients or other unidentified aspects of technique remains unclear. Interestingly, despite knowing of the higher extrusion rate with the hip site, nearly half the study participants still preferred that implant location for subsequent procedures.

The extrusion rate for the abdominal site (5%) in this study was lower than the extrusion rate in either of the previous studies conducted in this centre (Handelsman *et al*., 1997; Kelleher *et al*., 1999). The observation of between operator differences in adverse event rates in this study differs from previous retrospective (Handelsman *et al*., 1997) and prospective (Kelleher *et al*., 1999) studies at this centre, wherein

Table 3 Operator-related postprocedural adverse events

	n	Extrusion	Infection	Bruising
Operator 1	135	6 (4·4%)	3 (2·2%)	1 (0·7%)
Operator 2	80	13 (16·3%)	6 (7·5%)	2 (2·5%)
Other operator	31	2 (6·5%)	3 (9·7%)	2 (6·5%)
Total	246	21 (8·5%)	12 (4·9%)	5 (2·0%)
P		0·01	0·09	0·11

Table 4 Pharmacokinetic and pharmacodynamic variables from baseline until month 6 post implantation

	Total testosterone		Free testosterone		LH		FSH (IU/l)	
	Peak (nm/l)	AUC (nm/l × months)	Peak (pm/l)	AUC (pm/l × months)	Nadir (IU/l)	AUC (IU/l × months)	Nadir (IU/l)	AUC (IU/l × months)
Hip	25·8 ± 2·6	14 ± 1·6	503 ± 40	227 ± 17	1·5 ± 1	10 ± 2·1	6·5 ± 5·3	11·6 ± 3·9
Abdomen	24·6 ± 2·6	14·4 ± 1·3	435 ± 52	223 ± 20	1·1 ± 0·9	8·6 ± 1·1	7·1 ± 3·7	9·3 ± 0·9
P	0·35	0·83	0·36	0·92	0·79	0·73	0·32	0·62
Two-track	25·7 ± 2·8	13 ± 0·9	329 ± 27	197 ± 17	1·1 ± 0·9	9 ± 1·7	1·9 ± 1·4	11·8 ± 1·4
Four-track	24·7 ± 2·5	14·9 ± 1·3	272 ± 37	238 ± 19	1·3 ± 1	7·7 ± 1·4	7·1 ± 3·7	14·1 ± 1·5
P	0·92	0·83	0·43	0·5	0·9	0·72	0·51	0·19

no differences were found between operators, including those who performed most procedures in this study. Because all elements of the procedures are essentially unchanged, these variations in overall and operator-related extrusion rate are unexplained. One possibility for the lower abdominal extrusion rate is self-selection out of using pellets for androgen replacement by men who experienced extrusions, thereby decreasing the overall extrusion rate. This seems unlikely due to the high continuation rates with implants as well as there being no evidence that any men are more liable to repeated extrusions than by chance (Handelsman *et al*., 1997). This temporal trend in underlying extrusion rate again highlights the need for randomization in controlled clinical trials where the underlying event rate may vary.

This study also shows that using two rather than four tracks does not alter the likelihood of pellet extrusion. Prior to the study, we surmised that implanting two pellets, end-on-end, may have a higher extrusion rate than for pellets each in individual tracks because pellets implanted in that configuration are located closer to the point of insertion and/or because extrusion of the more distal pellet might expel two rather than one. However, this study has refuted these presumptions and the implantation procedure can be simplified. The pharmacokinetic and pharmacodynamic substudy results provide reassurance that the hormonal sequela from pellets implanted end-on-end is no different to pellets implanted in isolation, and therefore a two-track procedure does not significantly alter the release of testosterone. Therefore, as the two-track procedure causes less discomfort, is more time and resource efficient, and is preferred by patients than the traditional four-track insertion,

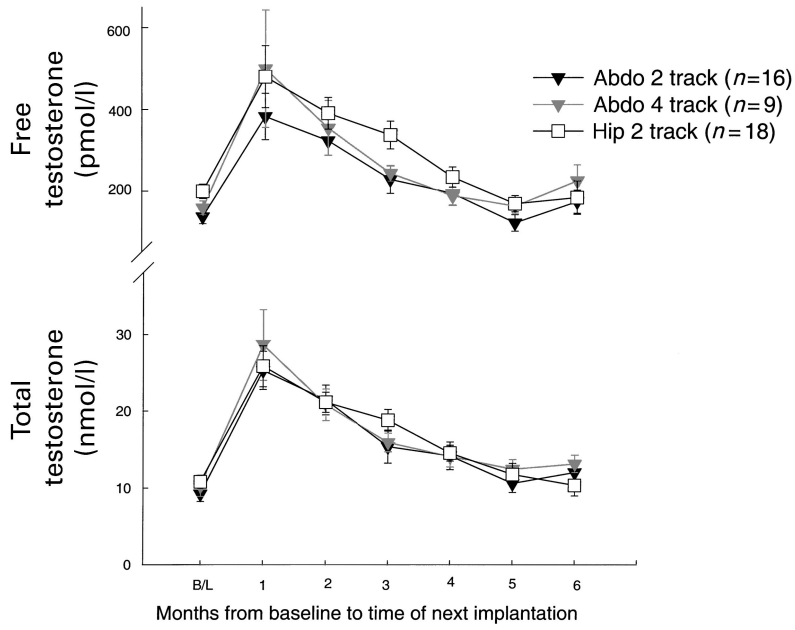

Fig. 1 Plasma free and total testosterone concentrations monthly from baseline to time of next scheduled implantation (month 6). Comparison is between standard four-track abdominal implantation and the two-track implantation site into the abdomen and hip sites. Data plotted as mean and standard error of mean.

it has become the new standard for routine use at this centre. A disappointing feature of the present study is that extrusion rate was not reduced. Further studies are underway to reduce extrusion rates which would further enhance testosterone pellet implants for long-term androgen replacement therapy.

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